details of their study, which are presented above. We welcome comments from readers.

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## Ciprofloxacin resistance in *Neisseria gonorrhoeae*: trends in Hawaii, 1997–2002

Sir—Kevin Fenton and colleagues May 31, p 1867)[1] report on the rapid increase in the prevalence of ciprofloxacin-resistant (CipR) gonococcal isolates in England and Wales between 1999 and 2002. Between 1997 and 1999 there was also a rise in the prevalence of CipR gonococcal isolates in Hawaii, from 1·4% to 9·5%.

In 1999, epidemiologists from the Hawaii State Department of Health (HDOH) and the US Centers for Disease Control and Prevention (CDC) initiated an investigation to assess risk factors for infection with CipR gonococcal isolates, and statewide gonococcal isolate surveillance was expanded to include military, public, and private laboratories. A case-control study revealed endemic transmission.[2] In 2000, the CDC advised that fluoroquinolones should no longer be used to treat gonorrhoea acquired in Hawaii.[3] The prevalence of CipR gonococcal isolates rose again in 2001, to 19·6%.[4]

Hawaii is somewhat unique in the USA, since it has a culture-based, statewide, state-subsidised gonorrhoeal screening programme. Every year more than 30 000 cultures are obtained from private and public providers. A key component of the state's screening and surveillance programme is the antibiotic sensitivity testing of all isolates by the HDOH laboratory. Since 1999, HDOH disease intervention specialists have prioritised interviewing of persons infected with CipR gonococcal isolates with the aim of timely identification, location, and treatment of sexual partners.[5] This aggressive statewide screening programme, coupled with active laboratory surveillance and disease-intervention/partner-notification activities, has resulted in a decline in the proportion of gonorrhoea cases with CipR isolates to 10·1% in 2002.

We agree wholeheartedly with Fenton and colleagues' recommendation for action, but would expand it to include, in addition to the review and revision of national and local treatment guidelines, an integrated approach, incorporating laboratory-based isolate surveillance with aggressive disease-intervention and partner-notification activities.

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## Do we need more iron-chelating drugs?

Sir—Eric Nisbet-Brown and co-workers (May 10, p 1597)[1] suggest that the initial clinical trial results of the iron-chelating drug ICL670 (4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic acid) are encouraging, although long-term safety and efficacy studies are needed. They also indicate that at the tolerated dose of 20 mg $kg^{-1}$ $day^{-1}$, ICL670 is an effective orally active iron chelator, because net iron excretion is just within the range of iron intake from standard transfusion regimens of 12–15 mL packed red-blood-cells $kg^{-1}$ $month^{-1}$. However, in the placebo group, mean net iron excretion is above zero and if this is taken into account ICL670 is not within the effective range of iron chelation.

Nisbet-Brown and colleagues also suggest that deferiprone is ineffective and that ICL670 at 20 mg $kg^{-1}$ $day^{-1}$ is more effective than deferoxamine. However, even at the highest dose of ICL670 used (40 mg $kg^{-1}$ $day^{-1}$), the mean daily iron excretion achieved is 23 mg for a 50 kg man, which is higher than 15 mg achieved at the 20 mg $kg^{-1}$ $day^{-1}$ dose, but much lower than that achieved with deferiprone or deferoxamine in patients who have thalassaemia, with mean daily iron excretion of 27 mg and 42 mg at doses of deferiprone of 75 mg/kg and 100 mg/kg, respectively.[2,3] The different pharmacokinetic profile of ICL670, including its slow rate of plasma clearance of half life of 12–16 h, limits the prospects of repeated administration and, consequently, its efficacy for iron removal.[4] The ferrokinetic profile of ICL670, which results mainly in an increase of faecal iron excretion, and its slow clearance from blood suggests accumulation of the drug, its metabolites, and iron complexes in lipid-soluble compartments of serum proteins and tissues and the inability of iron complexes to be cleared through the kidneys. Such properties increase the likelihood of toxic effects, similar to those of 8-hydroxyquinoline, which has similar lipophilicity to ICL670.[5] Lipophilic chelators similar to ICL670, including 8-hydroxyquinoline, also cause an increase in the absorption of iron.[4,5] A major drawback in understanding the ferrokinetic and pharmacodynamic characteristics of ICL670 is the absence of information about the isolation and characterisation of the metabolite(s) of ICL670, some of which may have iron-chelating properties. These characteristics may explain several unexplained observations in relation to unsaturated iron binding capacity (UIBC) in serum, why the results for total exposure to the drug as estimated by the area under the curve (AUC) were not proportional to the ICL670 dose; and why plasma concentrations of the iron complex Fe-$[ICL670]_2$ were not related to dose. Another concern about ICL670 is the cost to patients—only if it is cheaper than deferoxamine and deferiprone will it benefit most of the patients with thalassaemia in developing countries.[4]

The introduction of new iron-chelating drugs may ultimately improve iron-chelation therapy for patients with thalassaemia and other disorders. As with deferiprone or deferoxamine, patients with thalassaemia are expected to have variable response with respect to ICL670. Protocols to select the most effective and least toxic drug, or drug combinations, for each patient may increase the therapeutic benefits for